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Note

Silica gel supported chromium trioxide : An effective reagent for aromatization of 4-alkyl/aryl-1, 4-dihydropyridines

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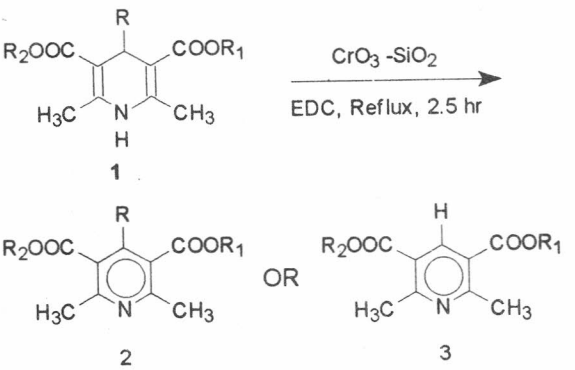
Oxidation of 4-aryl/alkyl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid diesters **1** has been carried out using silica gel supported CrO_3 reagent. The supported reagent is prepared by co-grinding, CrO_3 with silica gel in an agate mortar. In all the cases the corresponding aromatized product **2** is obtained in excellent yields (75-95%). Dealkylated product **3** obtained during oxidation of 4-isopropyl-1, 4-dihydropyridine.



It is known that 4-substituted-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid diethyl esters possess antihypoxics and antiischemic activities[1-3]. Furthermore, they are the starting materials for the synthesis of antibacterial agents[4,5].

The most common method of obtaining these compounds is by oxidation of the corresponding 4-substituted-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridine dicarboxylic acid diester. A large number of reagents are reported to bring about this oxidative aromatization. Nitrosonium cation generating reagents are known to oxidise 1, 4-dihydropyridines effectively[6-8]. Some other reagents used for this purpose are chloranil in benzene at reflux temperature[9], $SnCl_4$,[10] pyridine N-oxide[11], potassium permanganate in acetic acid[12]. Some chromium reagents have also been used to bring about this oxidation. Potassium dichromate with 10% sulphuric acid[9] and CrO_3 with acetic acid[13] bring about this oxidation. Pyridinium chlorochromate has also been reported to oxidise 1, 4-dihydropyridines but isolation of the product was very difficult[14]. Use of solid supported reagents is also reported. Major amongst them are the supported nitrates[15,16], MnO_2 supported on bentonite[17], and pyridinium chlorochromate on different supports[18].

We have recently reported the preparation of supported CrO_3 reagent by cogrinding method for selective oxidation of alcohols to the corresponding carbonyl compounds[19] and proved the reagent to be different from the reported one by characterization using Drift Spectra. The reagent showed an excellent shelf life of at least two months. It was thus tempting to take advantage of this reagent for aromatization of 1, 4-dihydropyridines. The aromatization of 4-aryl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid diester was carried out by stirring the reagent with the substrate in 1, 2-dichloroethane at reflux temperature for 2 hr and 30 min. The work up of reaction mixture involved mere filtration and washing the residue with hot solvent. The dehydrogenated product was obtained as the sole product, and the yields were quite high (75-90%) (cf. **Table I**).

The action of the reagent on 4-alkyl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid diester was of more interest, as many of the reported reagents gave either only dealkylated product or a mixture of dealkylated and dehydrogenated products. The aromatization of 4-methyl-1, 4-dihydropyridine **1i** with our reagent gave 2, 4, 6-trimethyl-3, 5-pyridinedicarboxylic acid dimethyl ester **2i** as the sole product in 79% yield. However, the aromatization of 4-isopropyl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid dimethyl ester gave 80% yield of the corresponding dealkylated pyridine derivative **3m**.

We also carried out aromatization of 4-(2-thienyl) substituted dihydropyridines to their corresponding dehydrogenated products in high yields (93-95%). The nature of the ester groups at 3 and 5 positions did not affect this aromatization.

Table I—Aromatization of 4-alkyl/aryl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridimedicarboxylic acid diesters **1** with silica gel supported CrO_3 reagent

Substrate	R	R_1	R_2	Product (Yield, %)
1a	C_6H_5	Me	Me	**2a**(88)
1b	4-OHC_6H_4	Me	Me	**2b**(73)
1c	4-$MeOC_6H_4$	Me	Me	**2c**(79)
1d	2-ClC_6H_4	Me	Me	**2d**(83)
1e	2-$NO_2C_6H_4$	Me	Me	**2e**(84)
1f	4-ClC_6H_4	Me	Me	**2f**(83)
1g	H	Me	Me	**2g**(82)
1h	H	Et	Et	**2h** (86)
1i	Me	Me	Me	**2i***(79)
1j	2-Thienyl	Me	Me	**2j** (92)
1k	2-Thienyl	Me	Et	**2k**† (94)
1l	2-Thienyl	Et	Et	**2l**(93)
1m	$(CH_3)_2CH$	Me	Me	**3m**‡(80)[a]

[a]Corresponding dealkylated product was obtained as the sole product.

*3, 5-Pyridinedicarboxylic acid, 2, 4, 6-trimethyl dimethyl ester **2i**. ^1H NMR($CDCl_3$): δ2.2(s, 3H, 4-CH_3). 2.5[s, 6H, 2, 6-$(CH_3)_2$] 3.9[s, 6H, 3, 5-$(COOCH_3)_2$].

†3, 5-Pyridinedicarboxylic acid, 2, 6-dimethyl-4-(2-thienyl)ethyl methyl ester **2k**. ^1H NMR($CDCl_3$): δ0.98(t, 3H, 3-$COOCH_2CH_3$) 2.5[s, 6H, 2, 6-$(CH_3)_2$]. 3.6(s, 3H, 5-$COOCH_3$), 4.1(q, 2H, 3-$COOCH_2CH_3$)), 7.0(m, 2H, thienyl ring protons) 7.3 (m, 1H, thienyl ring proton).

‡3, 5-Pyridinedicarboxylic acid, 2, 6- dimethyl dimethyl ester **3m**. ^1H NMR($CDCl_3$): 2.8[s, 6H, 2, 6-$CH_3)_2$] 3.9(s, 6H, 3, 5-$(COOCH_3)_2$] 5.9(s, 1H).

This method provides an attractive alternative for aromatization of 4-substituted-1, 4-dihydropyridines as the method of preparation of the supported oxidant is very easy, it has a good shelf life and can be stored easily. The reaction is clean and safe and product isolation is easy. The only drawback in this method is that the oxidant is required in 2.5 to 3 times excess, as is required in many other methods also.

General Procedure

Preparation of silica gel supported CrO_3 reagent. The reagent was prepared by co-grinding CrO_3 (1g, 10 mmol) and silica gel (4 g, SRL 230-400 mesh, surface area 385.6 m^2g^{-1}, pore volume 0.71 cm^{-1}) in an agate mortar. The yellow free flowing powder was then activated at 100°C for 4 hr and 30 min. The reagent attained a brown color. It can be used for oxidation or can be stored in a glass bottle and used by activating for 1 hr at 100°C whenever required.

Aromatization of 4-phenyl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid dimethyl ester. 4-Phenyl-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid dimethyl ester 1a (0.60 g, 2 mmoles) was dissolved in hot 1, 2-dichloroethane (15 mL) and the silica gel supported CrO_3 reagent (3 g, 6 mmoles) added to it. The mixture was stirred at reflux temperature for 2 hr and 30 min. The mixture was filtered and the residue washed with hot 1, 2-dichloroethane. The solvent was distilled off from the combined filtrates. A yellowish sticky solid was obtained which was triturated with petroleum ether to give a white free flowing powder of 4-phenyl-2, 6-dimethyl-3, 5-pyridinedicarboxylic acid dimethyl ester **2a** (0.52g, 88% yield).

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